REMARKS

Claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, and 36-46 are pending and under consideration in this application. All the pending claims stand rejected. After entry of the amendments made herein, claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, and 36-46 will be pending and under consideration in this application. None of the new claims and amendments made herein add new matter.

Telephone Conversation

Applicants thank the Examiner for her helpfulness in a telephone conversation with Applicants' undersigned representative on March 3, 2005. Applicants note that the Examiner agreed in the telephone conversation to have a telephone interview with Applicants' undersigned representative after she has received the present Amendment and Response.

35 U.S.C. § 112, second paragraph, rejection

Claims 36-43 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

From the comments on page 3, lines 7-12, of the Office Action, Applicants understand the Examiner's position to be that the term "sample of cells" lacks support in the specification and suggests replacing the term with "isolated population of cells".

Applicant respectfully submits that the term "sample", in the context of the claimed method at least, is equivalent to the term "preparation", which is supported by the specification (e.g., page 5, line 15) and claim 36 as originally filed. Nevertheless, in order to expedite prosecution of the application, Applicants have deleted the term "sample" and replaced it with the term "preparation". Applicants respectfully submit also that use of the word "population" would result in confusion because that term is applied to the cells that result from the method ("the population of claim 22"; see lines 1 and 11-12 of claim 36) whereas the cells at issue are the starting cells that are subjected to a transfection/transduction procedure resulting in this "population".

In the interest of even greater clarity and to conform it to its parent claims 1 and 22, Applicants have further amended claim 36 to require that the preparation of cells used for transfection/transduction contain T cells. This amendment is supported by the specification, e.g., at page 12, line 25, to page 15, line 18, and adds no new matter.

Applicants' undersigned representative would gladly discuss alternative wording for claim 36 with the Examiner if she so wishes.

Applicants respectfully submit that, in view of the above considerations and amendments, the rejection is moot.

35 U.S.C. § 103(a) rejections

(a) Claims 1, 2, 6, 9, 12, 15, 19-24, 34, 36-40, 42, 44, and 46 stand rejected as allegedly being unpatentable over Chen et al., in view of Kreitman et al., and as evidenced by Moreck et al.

Claims 4, 8, 11, 17, 18, 25, 41, and 45 stand rejected as allegedly being unpatentable over Chen et al., in view of Kreitman et al. and further in view of Chan et al. and Debinski et al.

Claims 5 and 11 stand rejected as allegedly being unpatentable over Chen et al., in view of Kreitman et al., and further in view of Sweeney et al.

Applicants respectfully traverse all the above rejections.

As in the prior response, the arguments presented against these rejections are "lack of motivation to combine" arguments. In order to make such arguments it is necessary that each reference be addressed separately, even though the rejection is based on a combination of references, in order to point to the failure of the each reference to provide the requisite motivation to combine.

The rejections of claims specifying a targeting cell, a population of cells, a method of treating a subject with cancer, and a method of making a cell population (i.e., claims 1, 2, 4-6, 8, 9, 11, 15, 17-25, 34, 36, 37, 44, and 46) are addressed separately from the rejections of claims specifying a viral vector (i.e., claims 38-42).

Claims 1, 2, 4-6, 8, 9, 11, 15, 17-25, 34, 36, 37, 44, and 46

From the comments on page 4, line 3, to page 5, line 10, of the Office Action, Applicants understand the Examiner's position to be that Chen et al. discloses every limitation of claim 1 except that cytokines or growth factors can be used as targeting moieties. Applicants respectfully disagree with this position for the following reasons.

Claim 1 specifies a cellular agent (targeting cell) that is composed of a T cell that has specificity ("significant binding affinity") for a cancer cell and that is transfected or transduced with a vector encoding a immunotoxic fusion protein having targeting domain and a toxic domain. Central to the invention, the claimed cellular agent has two levels of specificity. The first level of specificity is imparted by the cell's intrinsic specificity for a cancer cell. The second level of specificity is imparted by the targeting domain of the recombinantly expressed immunotoxic fusion protein, which contains a first member of an affinity pair (a cytokine, a growth factor, or a colony stimulating factor) that binds to a molecule on the surface of the cancer cell.

On the other hand, and with relevance to the comments on page 11, lines 1-3, of the Office Action, Chen et al. only discloses T cell cellular agents with a single level of specificity. First, it mentions normal, non-recombinant cytotoxic lymphocytes that have intrinsic tumor cell specific binding affinity only and, in particular to the difficulty in obtaining such "tumour-specific cytotoxic lymphocytes" (Abstract, lines 4-7). The article then indicates that they have solved this problem of obtaining tumor specific cytotoxic lymphocytes by making recombinant lymphocytes that have a single level of specificity endowed by the targeting domain (sFv) of a targeted toxin (Abstract, lines 7-10, and the rest of the article). Thus, the T cell cellular agents disclosed by Chen et al. have a single level of cancer cell specificity by virtue of EITHER (a) their intrinsic tumour specificity (as in the previously described tumor-specific cytotoxic lymphocytes) OR (b) the sFv antibody fragments in their recombinant targeted toxins (as in the genetically engineered cells described in the article). There is no teaching or even the least suggestion in Chen et al. of the desirability of making cellular agents with two levels of specificity, i.e., tumor-specific cytotoxic lymphocytes transfected or transduced with a vector

encoding an immunotoxin composed of a targeting domain and toxic domain. Indeed, making such cells would have involved precisely the problem its engineered cells were designed to avoid, i.e., obtaining tumor-specific cytotoxic lymphocytes (see above).

Moreover, none of the secondary references cited provides what is missing from Chen et al. in this regard. Kreitman et al., Chan et al., Debinski et al., and Sweeney et al. all disclose immunotoxins in which various cytokines are used as targeting domains. In none of the references is there any teaching or the least suggestion of the desirability of transforming any sort of targeting cells, let alone T cells with specific binding affinity for a cancer cell, with vectors encoding the immuntoxins.

With respect to the comments on page 4, lines 15-21, and page 10, lines 9-16, of the Office Action, Applicants submit that nowhere in Morecki et al. is it indicated that LAK cells contain T cells at all, let alone T cells with specific binding affinity for tumor cells. Morecki et al. describes: (a) tumor-infiltrating lymphocytes (TIL) (e.g., Abstract and page 344, column 1, to page 349, column 1), which Applicants acknowledge include tumor-specific cytotoxic T lymphocytes; and (b) CD4+ and CD8+ T cell populations highly purified from blood (e.g. Abstract, page 349, column 2, and page 350, column 1, including a description of the data shown in Table 7). The only mention of LAK cells in Morecki et al. is in regard to LAK cell culture supernatants (e.g., page 343, column 1, paragraphs 2 and 4).

Moreover, Applicants respectfully submit that Applicants' undersigned representative stated in the telephone interview on May 25, 2004, that LAK cells (as used for the experiments described on page 78, column 22, paragraph 3, to page 79, column 1, paragraph 1, of Chen et al). are largely, at least, NK cells rather than T cells and that any T cells present in the LAK cell preparations would be extremely unlikely to have specificity for tumor cells.

Furthermore, in experiments described in Chen et al. in which T cells were transfected with immunotoxin-encoding vectors, as pointed out in prior responses (on April 3, 2003, and June 1, 2004), the relevant T cells were human MOLT-4 acute lymphoblastic leukemia cells, which would not be expected to have specific binding affinity for tumor target cells.

In light of the fact that Chen et al. characterizes its recombinant cells made specific only by virtue of the tumor cell-specific targeting domains in the recombinant immunotoxins they express as "tumour-specific killer cells" (Abstract, lines 7-8), the use of the term "tumour-specific killer cells" in the title by no means suggests targeting T cells with two levels of specificity, i.e., T cells with intrinsic binding affinity for tumor cells transformed with a vector to express a recombinant immunotoxin that also binds to the tumor cells.

Thus, neither Chen et al. taken alone, or in combination with one or more of the secondary references, provides the motivation for one of ordinary skill in the art to transform a tumor-specific T cell with a vector encoding an immunotoxin containing any sort of targeting molecule, let alone a cytokine, a growth factor or a colony stimulating factor. For this reason alone, the above recited claims are not rendered obvious by the cited art.

However, in addition, Chen et al. contains no disclosure or even a suggestion of the desirability of replacing tumor-specific sFvs with cytokines (or growth factors and colony stimulating factors) in its targeting domains and none of the secondary references teach or even hint at the desirability of using any sort of targeting cells, let alone T cells, to deliver their immunotoxins. Thus, even if one of ordinary skill in the art would be persuaded by Chen et al. to make cellular agents with two levels of specificity (which for the reasons given above, she would not), such an artisan would not be motivated to replace the sFv employed by Chen et al. with any cytokine, growth factor, or colony stimulating factor, let alone the specific cytokines and growth factor disclosed by the cited secondary references.

Claims 38-42

From the comments on page 4, lines 21-22, of the Office Action, Applicants understand the Examiner's position to be that the combination of cited references renders obvious the claims specifying viral vectors encoding immunotoxins in which the targeting molecule is a cytokine, a growth factor, or a colony stimulating factor. Applicants respectfully disagree with this position.

Of the cited references, Chen et al. is the only one to mention a viral vector, i.e., a retroviral vector (e.g., page 78, column 2, paragraph 3, and the paragraph spanning pages 79 and

80). As pointed out above, Chen et al. does not mention or even remotely suggest the desirability of the replacing the tumor-specific sFv it employs in its immunotoxins with any other type of targeting molecule, let alone with the cytokines and growth factor used by the secondary references. Moreover, the only vectors employed by Kreitman et al. (e.g., page 466, column 1, paragraph 2), Chan et al. (e.g., page 1446, column 1, paragraph 2, to column 2, paragraph 1, and page 1448, column 1, paragraph 4, to column 2, paragraph 1), Debinsky et al. (e.g., page 14066, columns 1 and 2), and Sweeney et al. (e.g., page 202, columns 1 and 2, and page 2003, column 3) are plasmids and were used for the bacterial production of relevant immunotoxins. These secondary references made no mention or even a suggestion of the desirability of transforming mammalian cells with, or delivering to mammalian subjects, vectors encoding immunotoxins and to use viral vectors for such purposes. Thus, neither Chen et al. nor the secondary references contain the motivation to combine their respective disclosures and make viral vectors encoding immunotoxins containing cytokines, growth factors, or colony stimulating factors as targeting moieties.

(b) Claim 43 stands rejected as allegedly being unpatentable over Chen et al., in view of Kreitman et al., and further in view of Heslop et al. Applicants respectfully traverse the rejection.

From the comments on page 9, line 16, to page 10, line 7, of the Office Action, Applicants understand the Examiner's position to be that the combination of cited references renders obvious the claims specifying adenoviral and adenoassociated viral vectors encoding immunotoxins in which the targeting molecule is cytokine, a growth factor, or colony stimulating factor. Applicants respectfully disagree with this position.

The disclosure of Chen et al. and Kreitman et al. in regard to vectors is outlined above. Chen et al. does not suggest or even hint at using any viral vectors other than a retroviral vector and Kreitman et al. makes no disclosure or a suggestion of using of viral vectors at all. In a section that broadly discusses the use of "Improved Vectors" in gene transfer protocols, Heslop et al. briefly refers to the use of adenoviral and adenoassociated viral vectors (page 420, column

1, paragraphs 2 and 3). Nowhere in the article is there any mention or even a suggestion of the usefulness of immunotoxins of any sort, let alone those containing a sFv or a cytokine, growth factor, or colony stimulating factor as a targeting molecule. Thus, the cited references do not provide the motivation for one of ordinary skill in the art to combine the disclosures of the cited references and thence to make the viral vectors of claim 43.

In light of the above considerations, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that all of the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a petition for an automatic extension of time and a check in payment of the extension of time. Please apply any additional charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 11983-004001.

Respectfully submitted,

Date: 3/7/05

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